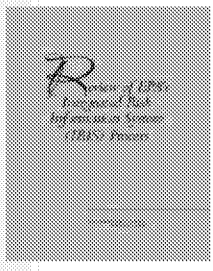
Updates from ORD National Center for Environmental Assessment (NCEA) & Integrated Risk Information System (IRIS)

Tina Bahadori, NCEA Director
Kris Thayer, NCEA IRIS Division Director

Briefing for the STPC
September 20, 2017

National Academy of Sciences (2014) Overarching Statements

2014



"Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the present committee's recommendations should be seen as building on the progress that EPA has already made." [p.9]

" . . . the IRIS program has moved forward steadily in planning for and implementing changes in each element of the assessment process. The committee is confident that there is an institutional commitment to completing the revisions of the process . . . Overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program." [p.135]

Appropriations Language

- **Report 114-281 Committee on Appropriations (June 16, 2016)**
  S.3068 - Department of the Interior, Environment, and Related Agencies Appropriations Act, 2017
- https://www.congress.gov/114/crpt/srpt281/CRPT-114srpt281.pdf
- IRIS (p. 63)
  - ✓ EPA to convene an interagency working group of relevant executive branch stakeholders and co-chaired with OIRA
  - ✓ Review compliance with NAS recommendations (2014)
    - Transition from single point estimates of hazard and exposure to distribution of estimated hazards, exposures, and risks, including central tendency values
    - Processes for evaluating study quality, relevance and risk of bias
    - Use of transparent and reproducible weight-of-evidence process
    - Selection of an adverse outcome
    - Use of default linear low-dose extrapolation and other default modeling approaches
    - Timetable for EPA's full implementation of NAS recommendations for all IRIS assessments
    - Report within 180 days

The IRIS Interagency Workgroup (IWG)

- IWG was convened in August 2017
- Co-chaired by EPA/ORD and OMB/OIRA – Richard Yamada overseeing.
  - Membership from across the federal family
- Has met twice and has a third meeting scheduled for the 25th of September.
- A brief Report to Congress (on the order of 2-3 pages) will be drafted, where we will summarize the meetings and actions, and plans moving forward.
- In addition, NCEA has requested the National Academies to hold a public meeting to evaluate IRIS's progress and to issue a consensus report within 6 months of that meeting. That report will also inform the IWG.

Broader Engagement

- **SAB**
  - **SAB Briefing, August 30, 2017**
    - **SAB letter to the Administrator about IRIS:** https://yosemite.epa.gov/sab/sabproduct.nsf/0/A9A9ACCE42B6AA0E8525818E004CC597/$File/EPA-SAB-17-008.pdf
    - "The SAB has observed significant enhancements in the IRIS program over the past few years, with impactful changes over the past year, and marked progress over the past six months."
    - "The changes are so extensive and positive that they constitute a virtual reinvention of IRIS."
    - "The SAB notes that no other federal entity performs the IRIS functions, and that IRIS helps ensure consistency in chemical assessments within the Agency and across the federal government."
  - **SAB Chemical Assessment Advisory Committee (SAB-CAAC) briefing scheduled for September 27-28, 2017**
- **Congressional hearing**
- **NAS**
  - **Agreement in place to peer review formaldehyde (Congressional requirement)**
  - **(possibly) arsenic**
- **Stakeholder outreach**
  - **Systematic review communities**
  - **Requests for correction**

IRIS Multi-Year Agenda

Developing Agenda

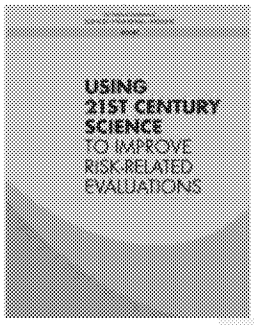
- **Released to the public December 2015**
- **Survey EPA program and regional offices for their assessment needs**
- **Estimate the resources needed for each assessment by science discipline**
- **Discuss with senior EPA officials how to meet the most high-priority needs**
- **Allocation of IRIS resources based on the plan**
- **Evaluate annually for continued relevance**

Group	Chemicals
1	Manganese
	Mercury/methylmercury
	Nitrate/nitrite
	Perfluoroalkyl compounds
	Vanadium and compounds
2	Acetaldehyde
	Ammonia (oral)
	Cadmium and compounds
	Uranium
3	Di-(2-ethylhexyl) phthalate
	Dichlorobenzene isomers
	Methyl t-butyl ether (MTBE)
	Nickel and compounds
	Styrene

How is IRIS Focusing?

- **Increase transparency and full implementation of systematic review**
  - implement using approaches that foster consistency across the IRIS program; many active and all new starts address ALL SR-related recommendations of 2014 NRC report
- **Modernize the IRIS Program**
  - through automation and machine learning to expedite systematic review, incorporation of emerging data types
- **Modularize product lines**
  - implement a portfolio of chemical evaluation products that optimize the application of the best available science and technology. These products will allow IRIS to remain flexible and responsive to clients within the EPA as well the diverse collection of stakeholders beyond EPA, including states, tribal nations, and other federal agencies.
- **Enhance accessibility**
  - provide outreach and training to make systematic review practices ubiquitous and more accessible; enhance data sharing through publicly available software platforms for assessments developed by EPA, other federal and state agencies, industry, academia and other third-parties.

Other IRIS Improvements

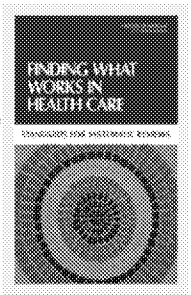


Next Generation IRIS

- IRIS in the 21st Century – implement recommendations of the NAS 2017 report, Using 21st Century Science to Improve Risk-Related Evaluations;
- Collaborate with EPA's National Center for Computational Toxicology (NCCT) to build expert-judgement case studies that inform assessment development and fill gaps in assessments, especially for data poor chemicals; inform where resources should be strategically invested to generate additional data.

Improved Management Practices

- Create efficiencies – engage other agencies to share common practices, data, and tools, and more efficiently leverage resources across the federal government.
- Improve timeliness and responsiveness – deploy program and project management tools to more effectively and efficiently utilize human resources to ensure timely delivery of products.



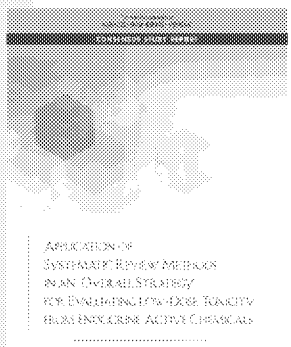
A structured and documented process for transparent literature review[1,2]

"… systematic review is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent"

[1] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. EPA-HQ-OPPT-2016-0654. https://www.epa.gov/sites/production/files/2017-06/documents/prepubcopy_tsca_riskeval_final_rule_2017-06-22.pdf

[2] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

NAS (2017): Reflections and Lessons Learned from the Systematic Review



- "….one disadvantage in conducting a systematic review is that it can be time and resource intensive, particularly for individuals that have not previously conducted a systematic review." [p.157]
- "The committee discussed at length whether it could provide EPA with advice about when a systematic review should be performed but decided it could not be more specific because that decision will depend on the availability of data and resources, the anticipated actions, the time frame for decision making, and other factors." [p.157]
- "The committee also recognized that it might be advantageous for EPA to build on existing systematic reviews that are published in the peer-reviewed literature." [p.157]
- "The committee recognizes that the methods and role of systematic review and meta-analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions." [p.157]

Making Systematic Review Pragmatic and Feasible For IRIS

- Standard operating procedures (IRIS Handbook) and chemical-specific protocols
- Use of specialized software applications and automation
- Targeted focus, especially for evidence-rich topics
  - Make better use of well-conducted existing assessments as starting point
- Multiple assessment products ("modularity")
- Solicit early feedback during scoping and problem formulation via assessment plans
  - Summary of scoping and initial problem formulation conclusions, objectives and specific aims of the assessment, draft PECO (Population, Exposure, Comparators, and Outcomes) framework that outlines the evidence considered most pertinent to the assessment, and identification of key areas of scientific complexity
- Utilize iterative protocols to ensure focus on best-available and most-informative evidence as the assessment progresses

Protocol: Literature Searching and Screening

basic practices

special topics

4. LITERATURE SEARCH AND SCREENING STRATEGIES

4.1. USE OF EXISTING ASSESSMENTS

Describe any use of existing assessments that serve as starting points for the literature search.

4.2. LITERATURE SEARCH STRATEGIES

Literature search strategies were developed using key terms and words relate statement. Development of the search strategy for each topic area were conducted b relevant search terms through (1) reviewing PubMed's Medical Subject Headings (M relevant and appropriate terms, (2) extracting key terminology from relevant review previously identified primary data studies that are known to be relevant to the topic and

4.3. UNPUBLISHED DATA

IRIS only includes publicly accessible, peer-reviewed information in its evaluations. However, it is possible that unpublished data directly relevant to the PECO statement may be identified during the course of the assessment. In this case, EPA is able to obtain external peer review if the owners of the data are willing to have the study details and results made publicly accessible. The peer review would include an evaluation of the study similar to that for peer review of a journal publication. The EPA would identify and select two to three scientists knowledgeable in scientific disciplines relevant to the topic as potential peer reviewers. Persons invited to serve as peer reviewers would be screened for conflict of interest (COI) prior to confirming their service. In most

4.4. SCREENING PROCESS

Studies that comply with the criteria specified in the PECO inclusion while those that do not meet these criteria will be exclude the exclusion criteria noted below will be applied. However, the refer will be reviewed to identify PECO-relevant studies that may have been searching.

- Records that do not contain original data, such as reviews, editorials,
- Studies that have not been peer-reviewed (e.g., conference abstracts theses/dissertations, working papers from research groups or committees, and white papers).
- {others decided by the assessment team}

Studies will be screened for inclusion using a structured form in {list the software application and URL, or product site, e.g., DistillerSR (Evidence Partners,

4.4.1. Multiple publications of the same data

Multiple publications with overlapping data for the same study (e.g., publications reporting subgroups, additional outcomes or exposures outside the scope of an evaluation, or longer follow-up) can be identified by examining author affiliations, study designs, cohort name, enrollment criteria, and enrollment dates. If necessary, study authors will be contacted to clarify any uncertainty about the independence of two or more articles. IRIS will include all publications on the study, select one study to use as the primary, and consider the others as secondary publications with annotation as being related to the primary record during data abstraction. The primary study

Protocol: Study Evaluation (Epidemiology)

6.2. EPIDEMIOLOGY STUDY EVALUATION

Evaluation of epidemiology studies to assess bias and study sensitivity will be conducted for the following domains: exposure measures, outcome measures, participant selection, potential confounding, analysis, selection of reported results, and study sensitivity (Table 2):

Table 2. Domains of evaluation for epidemiology studies

Domain	Example information
Exposure measures	Source(s) of exposure (consumer products, occupational, an industrial accident) and s exposure data, blinding to outcome, level of detail for job history data, when measure were taken, type of biomarker(s), assay information, reliability data from repeat meas studies, validation studies.
Outcome measures	Source of outcome (effect) measure, blinding to exposure status or level, how measured/classified, incident versus prevalent disease, evidence from validation studi prevalence (or distribution summary statistics for continuous measures).
Participant selection	Study design, where and when was the study conducted, and who was included? Se process, exclusion and inclusion criteria, type of controls, total eligible, comparison be participants and nonparticipants (or followed and not followed), final analysis group Were studies include potential vulnerable/susceptible groups or lifestages?
Potential confounding	Background research on key confounders for specific populations or settings; particip characteristic data, by group; strategy/approach for consideration of potential confou strength of associations between exposure and potential confounders and between p confounders and outcome; degree of exposure to the confounder in the population.
Analysis	Extent (and if applicable, treatment) of missing data for exposure, outcome, and confo approach to modeling, classification of exposure and outcome variables (continuous v categorical), testing of assumptions, sample size for specific analyses, relevant sensiti analyses.
Selective reporting	Are results presented with adequate detail for all of the endpoints of interest? Are re presented for the full sample as well as for specified subgroups? Were stratified analy modification) motivated by a specific hypothesis?
Sensitivity	What exposure range is spanned in this study? What are the ages of participants (e.g., young in studies of pubertal development)? What is the length of follow-up (for outco long latency periods)? Choice of referent group and the level of exposure contrast bet groups (i.e., the extent to which the "unexposed group" is truly unexposed, and the de of exposure in the group designated as "exposed").

The principles and framework used for the evaluation of epidemiology studies are based Cochrane Risk of Bias in Non-randomized Studies (ROBINS) of Interventions (ROBINS-I) (al., 2016) but modified to address environmental and occupational exposures. The underl philosophy of ROBINS-I is to describes attributes of an "ideal" study with respect to each evaluation domains (e.g., exposure measurement, outcome classification, etc.). Core and prompting questions are used to collect information to guide evaluation of each domain. In addition, expected

Table 3. Example question specification for evaluation of domains in epidemiology studies

Core question	Example prompting questions	Example follow-up questions
Exposure Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?	For all: • Does the exposure measure capture the major source(s) of variability in exposure among the participants, considering intensity, frequency, and duration of exposure? • Does the exposure measure reflect a relevant time window? If not, can the relationship between measures at this time and the relevant time window be estimated reliably? • Was the exposure measurement likely to be affected by a knowledge of the outcome or by the presence of the outcome (i.e., reverse causality)? For case-control studies of occupational exposures: • Is exposure based on a comprehensive job history describing tasks, setting, time period, and use of specific materials? For biomarkers of exposure, general population: • Is a standard assay used? What are the intra- and inter-assay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? • What exposure time-period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?	Is the degree of exposure misclassification likely to vary by exposure level? If the correlation between successive measurements is moderate, is there an adequate statistical approach to ameliorate variability in measurement? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
Outcome Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?	For all: • Is disease ascertainment likely to be affected by knowledge of or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)? For case-control studies: • Is the non-diseased comparison group (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease? For mortality measures: • How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease? For diagnosis of disease measures: • Is diagnosis based on standard clinical criteria? If based on reabstract of records, what is the validity of this measure?	Is there a concern that any outcome misclassification is non-differential, differential, or both? What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Protocol: Study Evaluation (Animal)

Table 4. General criteria to evaluate outcomes from animal toxicology studies

Domain	Metric	Criteria
Reporting Quality	Reporting of information necessary for study evaluation	Key information necessary for study evaluation (study would be deemed critically deficient if not reported*): ▪ Species, test article dose, endpoints investigated; Important information, which st brackets contain secondary infor based on the needs of a given st information. ◆ *Test animal* – strain; sex (e.g., housing, feed, end procedures); age or dos ◆ *Exposure methods* – test route of administration; volume, exposure chara verification methods); ◆ *Experimental design* – g during exposure and e acclimation(s) (e.g., litter ▪ *Endpoint evaluations* – were measured, proced and negative controls; s region of tissues/ organs (e.g., surgery, co-treatm ◆ *Results presentation* – were investigated; infor assessed, sample size, s maternal toxicity in dee in long-term bioassays) * Although such decisions should information is not reported, it is authors. However, for other rele confidence conclusions if it does not to study authors. Note: Studies adhering to GLP (o established by (inter)national or quality.
Selection or Performance Bias	Allocation of animals to experimental groups	Ideally, animal studies are rando chance of being assigned to any allocation procedures sufficiently In good, are studies indicating so exposure, for example according of randomization. The least prefe how groups were assigned.
	Blinding of investigators, particularly during outcome assessment	Good studies will conceal the tre the endpoint evaluations (and, a personnel and technicians). Both outcome measures are more obj

Domain	Metric	Criteria
		weight(s) or measurement is automated using computer-driven systems (e.g., as is the case in many behavioral assessments).
Confounding/Variables Control	Control for variables across experimental groups	In a good study, outside of the (chemical) exposure of interest, all variables will be controlled for and consistent across experi additional variables introduced interdirectly mitigated by knowledge or inferences regard which the variable can influence the endpoi A very important example to consider is whe controlled to attribute the effects of exposu alone. Generally, well-conducted exposures exposures and will include experimental con confounding (e.g., use of a suitable vehicle o Other examples of variables that may be inc experimental groups include, protective or ill secondary effects, diet composition; sacrifice
Reporting or Attrition Bias	Lack of selective data reporting and unaccounted for loss of animals	In a good study, information is reported on g comparisons for all animals, across treatmen Aspects to consider include whether all study results (if not, are explanations, such as deat provided), and whether expected comparisons from the analyses. In some studies, the numb (e.g., a suite of standard measures in a guide Note: This metric does not address whether considers statistical test methods.
Exposure Methods Sensitivity	Characterization of the exposure to the compound of interest	Consider whether there are notable issues th of the exposure levels, or of exposure to the on the chemical being assessed, that may inf stability and composition (e.g., purity; isome exposure generation and analytic verification tested levels and spacing between exposure methods); and details of exposure methods (e.g., dosage volume). In some cases, exposure bio treated animals can mitigate concerns regard on the validity of the biomarker for the chem Note: While this identifies uncertainties in de valid reason for exclusion from Hazard ID.
	Utility of the exposure design for the endpoint of interest	Based on the known or presumed biological evaluated, consider whether there are notab frequency, or duration of exposure. For exam will cover a greater proportion of the develo critical to the system of interest, while better other chronic outcomes will be of longer dur infrequently or sporadically, or, conversely, d depending on the exposure level, can incre
Endpoint Assessment and Results Display	Sensitivity and specificity of the endpoint evaluations	Consider whether there are notable concerns about aspects of the procedures for, or the finding of, the endpoint evaluations. Based on the endpoint evaluation protocol used for the endpoints of interest, specific considerations will typically include: ▪ Concerns regarding the sensitivity of the specific protocols for evaluating the endpoint of interest (i.e. assays can differ dramatically in terms of their ability to detect effects), and/or their timing (i.e. the age of animals at assessment can be critical to the appropriateness and sensitivity of the evaluations). This includes both over-estimates or underestimates of the true effect, as well as a much higher (or lower) probability for detecting the effect(s) being assessed. ▪ Concerns regarding the specificity and validity of the protocols. This includes the use of appropriate protocol controls to rule out non-specific effects, which can often be inferred from established guidelines or historical assay data. It may be considered useful for assessing, consider, or novel protocols to include positive and/or negative controls. ▪ Concerns regarding adequate sampling. This includes both the experimental unit (e.g., litter, animal) and endpoint (e.g., number of slides evaluated). This is typically inferred from historical knowledge of the assay or comparable assays. Notes: Human relevance of the endpoint is not addressed during study evaluation; for under sampling without blinding (e.g., sampling bias), this will typically lead to gross overestimates of effect; sample size is generally not a reason for exclusion.
	Usability and transparency of the presented data	Consider whether the results are analyzed or presented in a way that limits concerns regarding the reliability of the findings. Items that will typically be important to consider include: ▪ Concern that the level of detail provided does not allow for an informed interpretation of the results (e.g., authors' conclusions without quantitative data; discussing neoplasms without distinguishing between benign and malignant tumors; over-presenting variability). ▪ Concern that the way in which the data were analyzed, compared, or presented is inappropriate or misleading. Examples include: failing to control for litter effects (e.g., when presenting pup data rather than the preferred litter data); pooling results from males and females or across lesion types; failing to address observed or presumed toxicity (e.g., in assessed animals or cases) when exposure levels are known or expected to be highly toxic; incomplete presentation of the data (e.g., presenting continuous data as dichotomized), or non-preferred display of results (e.g., using a different response than is expected for that assay). The evaluator should support how or why, and to what extent, this might mislead interpretations. Notes: Concerns regarding the statistical methods applied are not addressed during study evaluation, but should be flagged for review by a statistician. Missing information related to this metric should typically be requested from study authors.

Protocol: Study Evaluation (General Approach)

6.1. STUDY EVALUATION OVERVIEW

The general approach (described in this section) of study evaluation for epidemiology and animal studies is the same, but the specifics of applying the approach differ and thus they are described separately in the following sections (Sections 6.2 and 6.3).

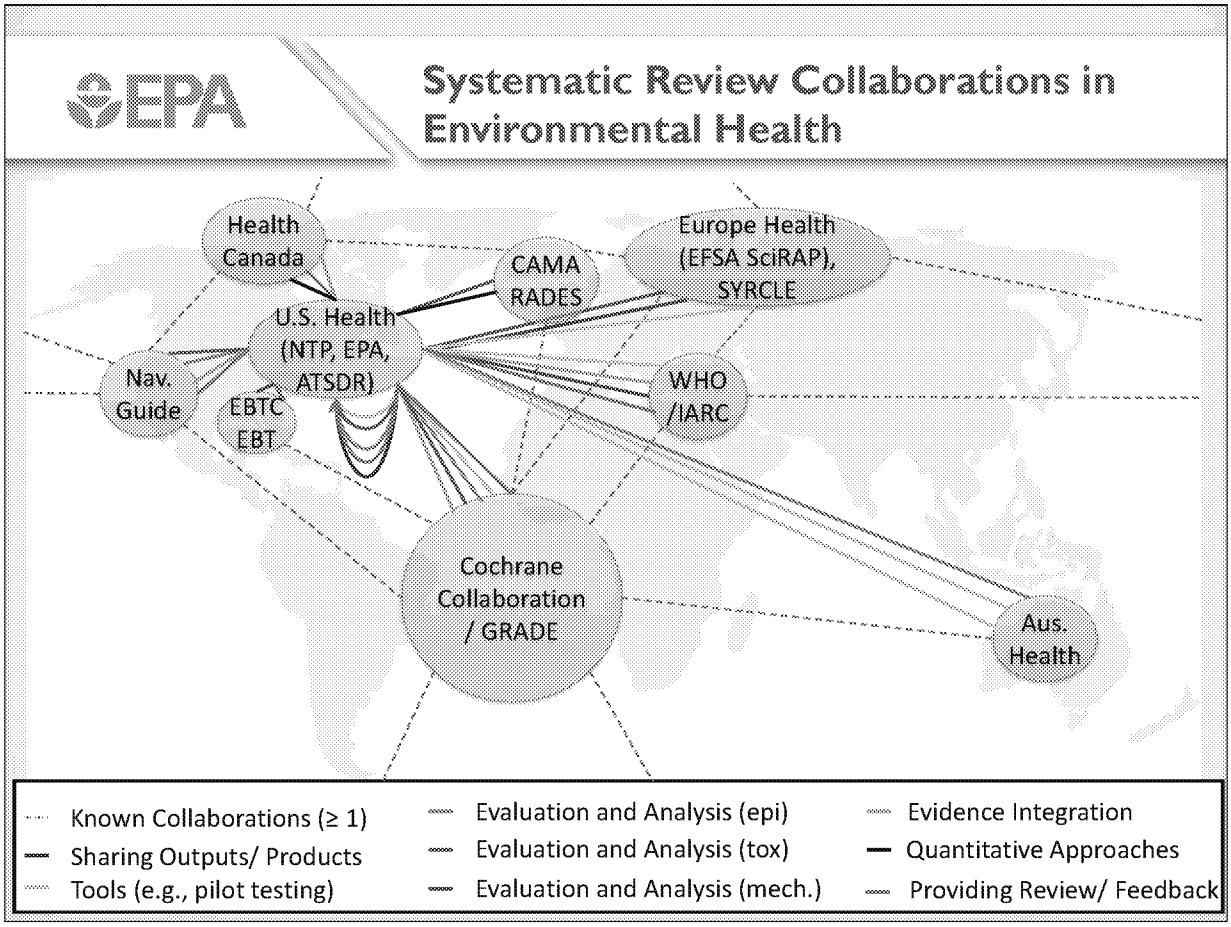
The evaluation will be conducted independently by at least two reviewers. For studies that examine more than one outcome, the evaluation process will be outcome or endpoint-specific, as the details may vary for the different endpoints.

For each study[6] (specifically, an outcome or group of related outcomes reported in a study or in a sample within a study), in each domain, reviewers will reach a consensus judgment of **Good**, **Adequate**, **Poor**, or **Critically Deficient**. It is important to stress that study evaluation is performed in the context of the study's utility for hazard identification of individual outcomes. While limitations specific to the usability of the study for dose-response analysis are noted (to inform those later decisions), they do not contribute to the study confidence judgments. These terms are defined as follows:

- "Good" is intended to represent a judgment that there was appropriate conduct relating to the domain, and any minor deficiencies that were noted would not be expected to influence the study results.
- "Adequate" indicates a judgment that there were experimental limitations in the domain, but that those limitations are not likely to be severe or to have substantial impact on the results.
- "Poor" denotes identified biases or deficiencies that are interpreted as having substantial impact on the results or which prevent reliable interpretation of the findings.
- "Not reported" indicates that the information necessary to evaluate the domain was not available in the study. Generally, this term carries the same functional interpretation as "Poor" for the purposes of the study confidence classification, based on the number and severity of other limitations identified in the study. It may or may not be worth reaching out to the study authors for this information (see discussion below).
- "Critically Deficient" reflects a judgment that the experimental conduct relating to the domain in question introduced a flaw so serious that the study should not be used without

Once the evaluation domains have been considered, the identified strengths and limitations will be combined to reach a study confidence classification of **High**, **Medium**, **Low**, or **Uninformative**. This classification will be based on the reviewer judgments across the evaluation domains, and will include consideration of the likely impact of the noted deficiencies in bias and sensitivity, or inadequate reporting, on the results. The classifications, which reflect a consensus judgment between reviewers, are defined as follows:

- **High Confidence:** No notable deficiencies or concerns were identified; the potential for bias is unlikely or minimal, and the study used sensitive methodology. In general, although classifications are not decided by "scoring", high confidence studies would reflect judgments of good across all or most evaluation domains.
- **Medium Confidence:** Possible deficiencies or concerns were noted, but the limitations are unlikely to be of a substantive degree. Generally, medium confidence studies will include adequate or good judgments across most domains, with the impact of any identified limitation not being judged as severe.
- **Low Confidence:** Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation. Typically, low confidence studies would have a poor evaluation for one or more domains (unless the impact of the particular limitations on the results is judged as unlikely to be severe).
- **Uninformative:** Serious flaw(s) make the study results unusable for informing hazard identification. Studies with critical deficiencies in any evaluation domain will almost always be classified as uninformative (see explanation above). Studies with multiple poor judgments across domains may also be considered uninformative, particularly when there is a robust database of studies on the outcome(s) of interest or when the impact of the limitations is viewed as severe.


EPA
Systematic Review Collaborations in Environmental Health
Health Canada
CAMA
RADES
Europe Health (EFSA SciRAP), SYRCLE
U.S. Health (NTP, EPA, ATSDR)
Nav. Guide
EBTC
EBT
WHO /IARC
Cochrane Collaboration / GRADE
Aus. Health
Known Collaborations (≥ 1)
Sharing Outputs/ Products
Tools (e.g., pilot testing)
Evaluation and Analysis (epi)
Evaluation and Analysis (tox)
Evaluation and Analysis (mech.)
Evidence Integration
Quantitative Approaches
Providing Review/ Feedback

IRIS Assessment Plan Outline

- How the IRIS Assessment Plans (IAPs) fit into the 7-Step IRIS process for developing human health assessments
- Increased development and transparency of systematic review materials, including scoping & problem formulation materials
- IAPs: what they are intended to be, and what they are not
- Application of IAPs in the creation of later systematic review materials to support draft development

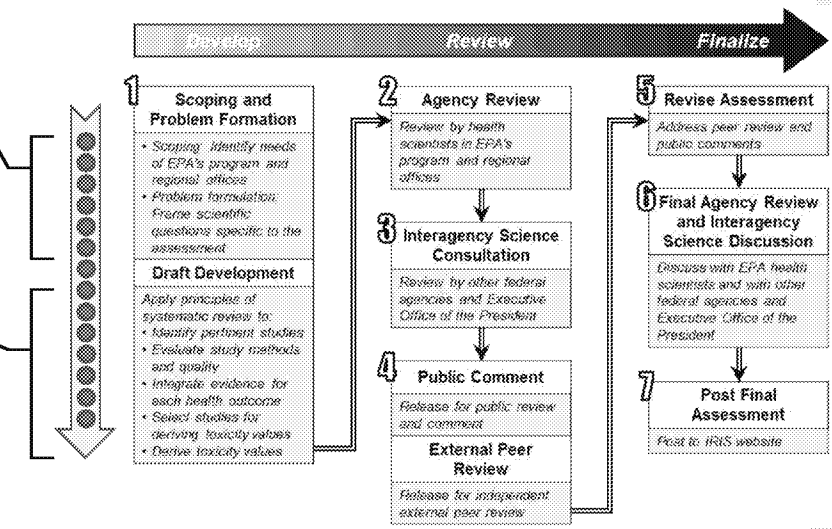
IRIS Assessment Plans in the 7-Step IRIS Process

IRIS Assessment Plans (IAPs)

- What the assessment will cover

Systematic Review Protocols

- How the assessment will be conducted



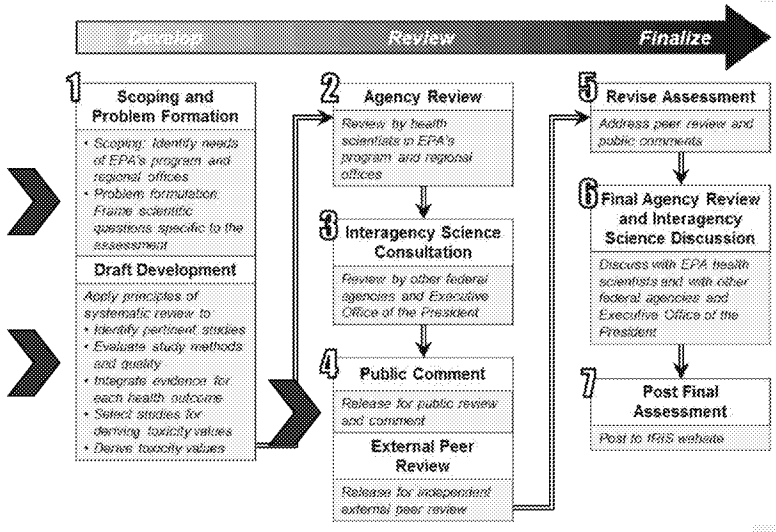
https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process

Transparency in the IRIS Assessment Process

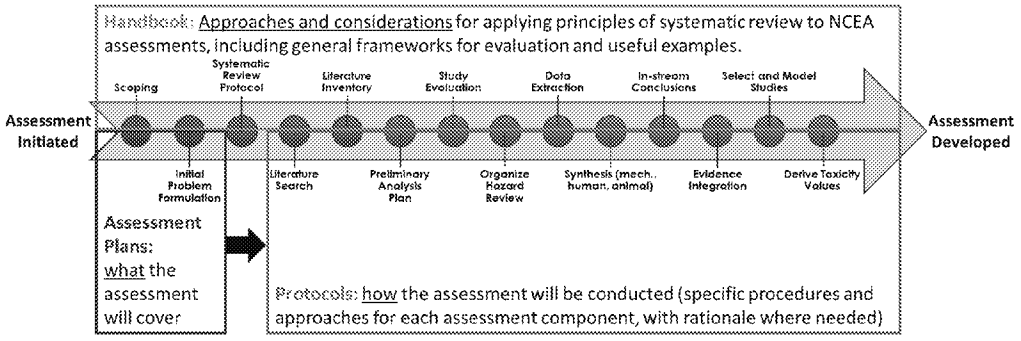
Assessment materials will be made available for public comment at various stages in development

- Early Step 1: IRIS Assessment Plans (IAPs)
  - For ethylbenzene, nitrate/nitrite, and chloroform
    - The federal docket for public comment is open:

    [TBD ~ 09/11 – 10/10]
- Mid-Step 1: Systematic Review Protocols
- Step 4: Public Discussion Assessment Draft

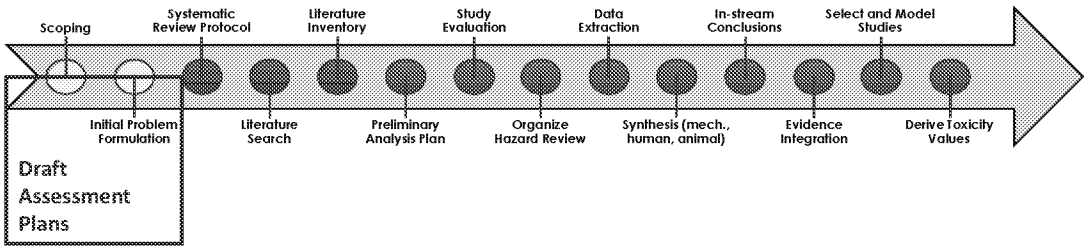


Assessment Plans and Protocols in the Drafting Process



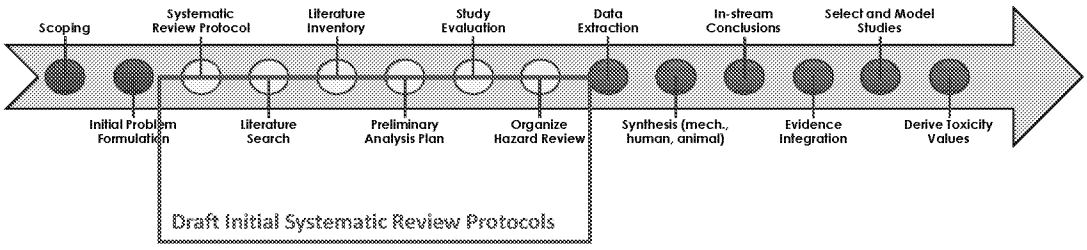
- Assessment development illustrated as sequential steps in the systematic review process, which will promote consistency and transparency across the IRIS program products
- General standard operating procedures will be described in the IRIS Program Handbook, while detailed approaches tailored to each assessment are described in the chemical-assessment specific plans and protocols

Role of Draft IRIS Assessment Plans (IAPs)

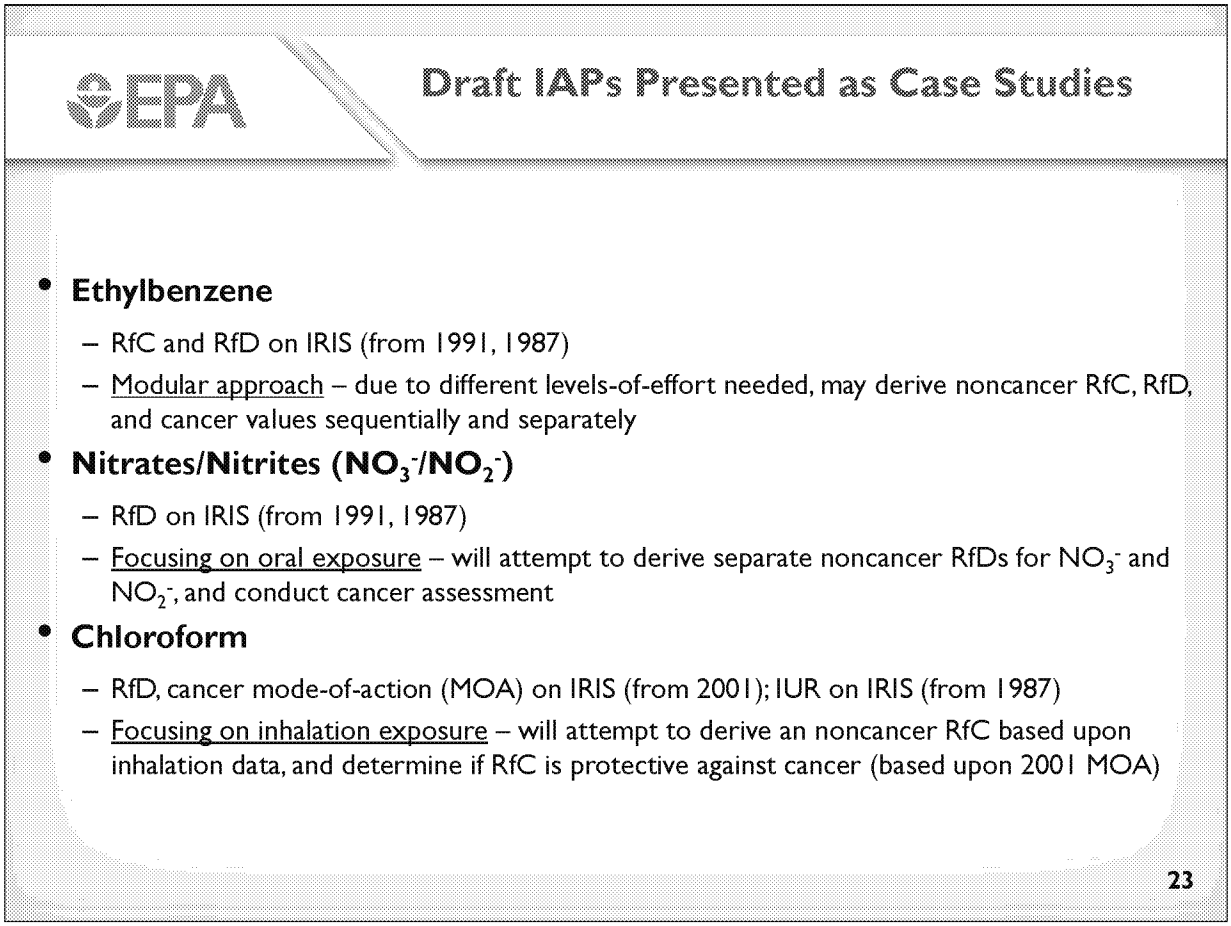


- As the INITIAL step in problem formulation, IAPs summarize:
  - Scoping and initial problem formulation conclusions
  - Objectives, and specific aims
  - Draft PECO (Population, Exposure, Comparators, and Outcomes) framework
  - Identification of key areas of scientific complexity

IAPs Become the Foundation for the Systematic Review Protocols



- The initial systematic review protocol will be made publicly available after review of draft IAPs
  - Protocol details how the work described in the IAP will be conducted
  - Also captures changes to IAP in response to comments received
- Protocol is iterative; the focus will be on the best available and most informative evidence
  - Public science sessions may be needed to address complex scientific issues, and refine the protocol

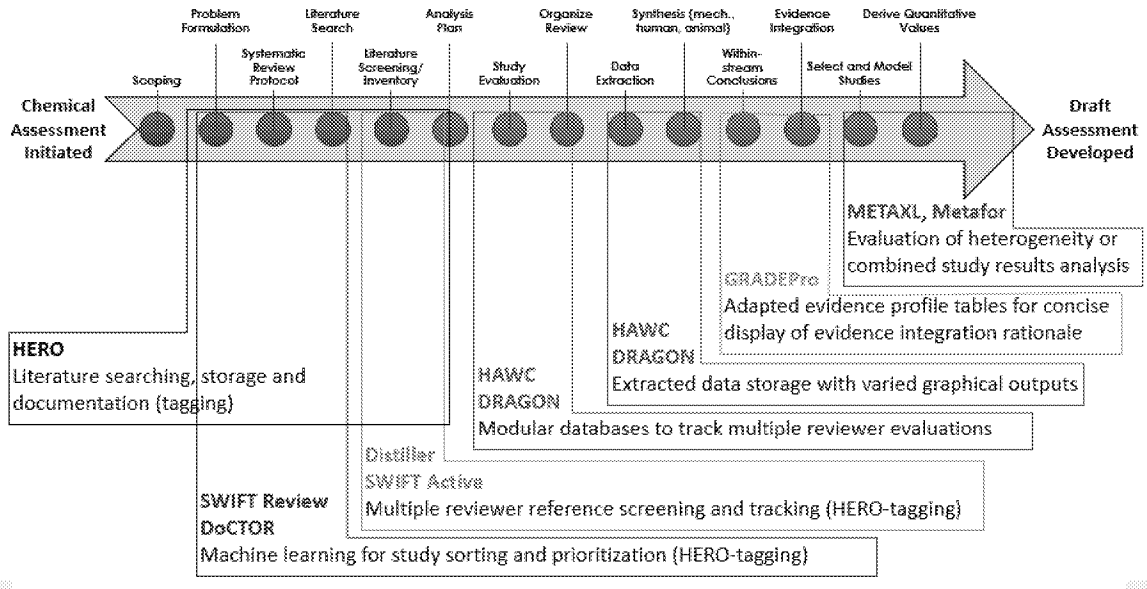


May be questions on why ethylbenzene is being presented as scoping and problem formulation materials again; confirming that Agency need exists and that it matches EPA priorities.

Open Discussion

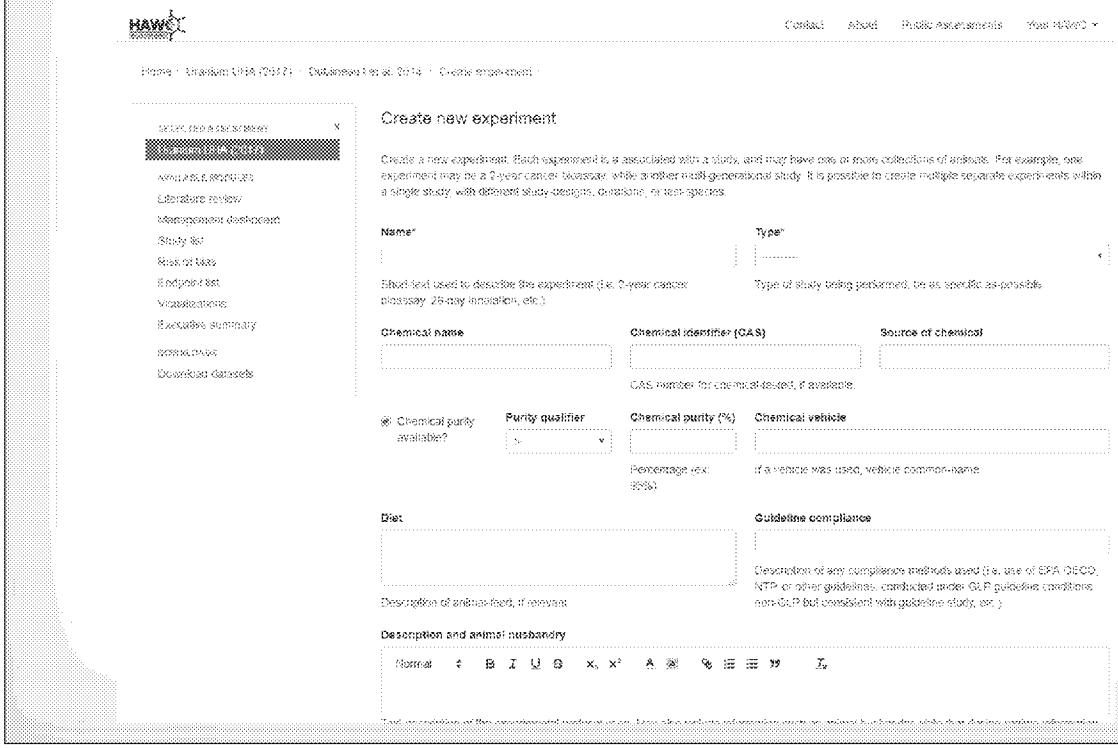
Backup Slides

Systematic Review Tools



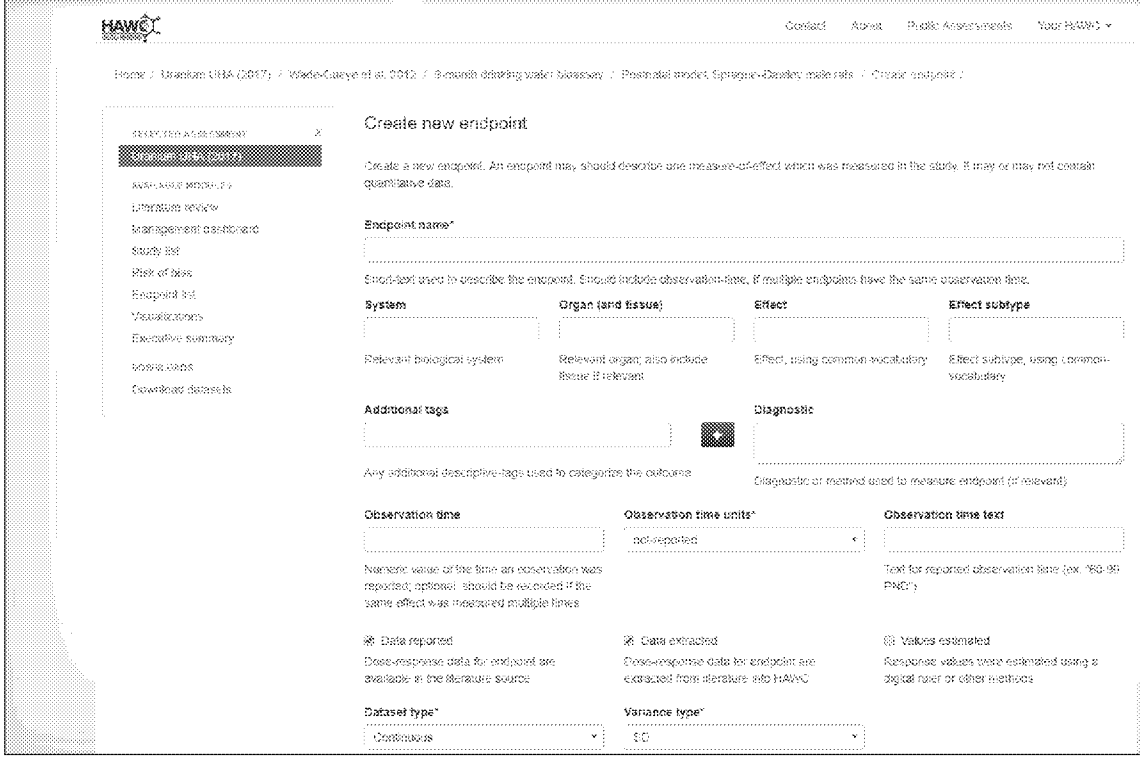
Tools repository: systematicreviewtools.com

HAWC: Data Extraction Animal Bioassay

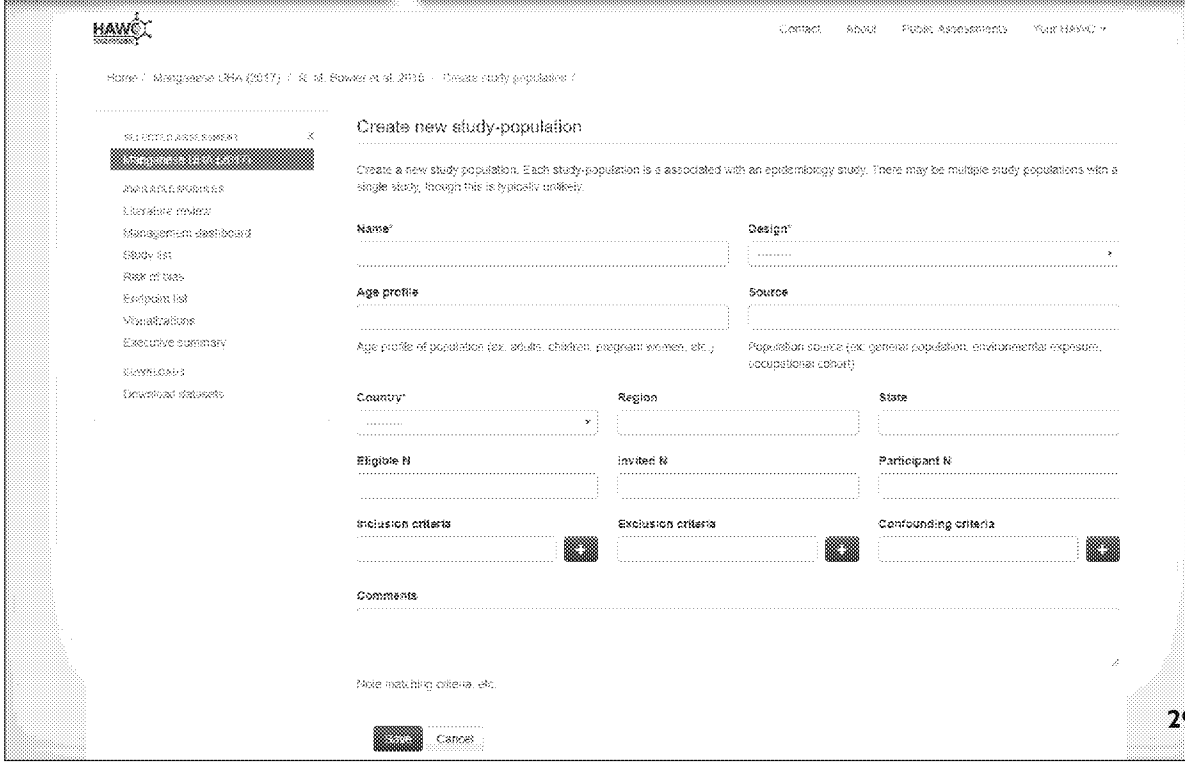


27

HAWC: Data Extraction Animal Bioassay



HAWC: Data Extraction Epidemiology



Epidemiology: Click to See More Display

"Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid"

Draft: Eczema, Prospective Studies

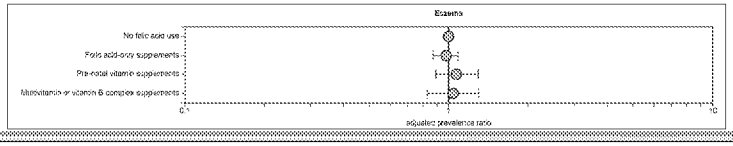
Study	Population Name	Assessed Outcome Nam	Exposure Measure	Exposure Comparison Statistical
Bekkers, 2012	PIAMA birth cohort, 1996-1997	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Magdeleijns, 2011	KOALA Birth Cohort Study	Eczema until		
Magdeleijns, 2011	KOALA Birth Cohort Study	Eczema until		
Magdeleijns, 2011	KOALA Birth Cohort Study	Eczema until		

Bekkers, 2012 / PIAMA birth cohort, 1996-1997 / Folic acid containing supplements during pregnancy / Eczema

Assessed outcome	Eczema
Population description	PIAMA birth cohort, 1996-1997
Diagnostic	self-reported
Diagnostic description	an itchy rash that came and went on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles)
Risk finding supported?	inconclusive
Prevalence /incidence	0.180 - 0.142, reported by age (Table 2)
Statistical metric presented	adjusted prevalence ratio
Statistical metric description	Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements on the same individual. An independent correlation structure was used; now? for the other outcome measures. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age.
Statistical power sufficient?	not reported or calculated
Dose response trend?	not applicable
Effect tags	clinical, hypersensitivity, immunological
Adjustment factors	• maternal allergy • maternal education • maternal smoking during pregnancy • number older siblings

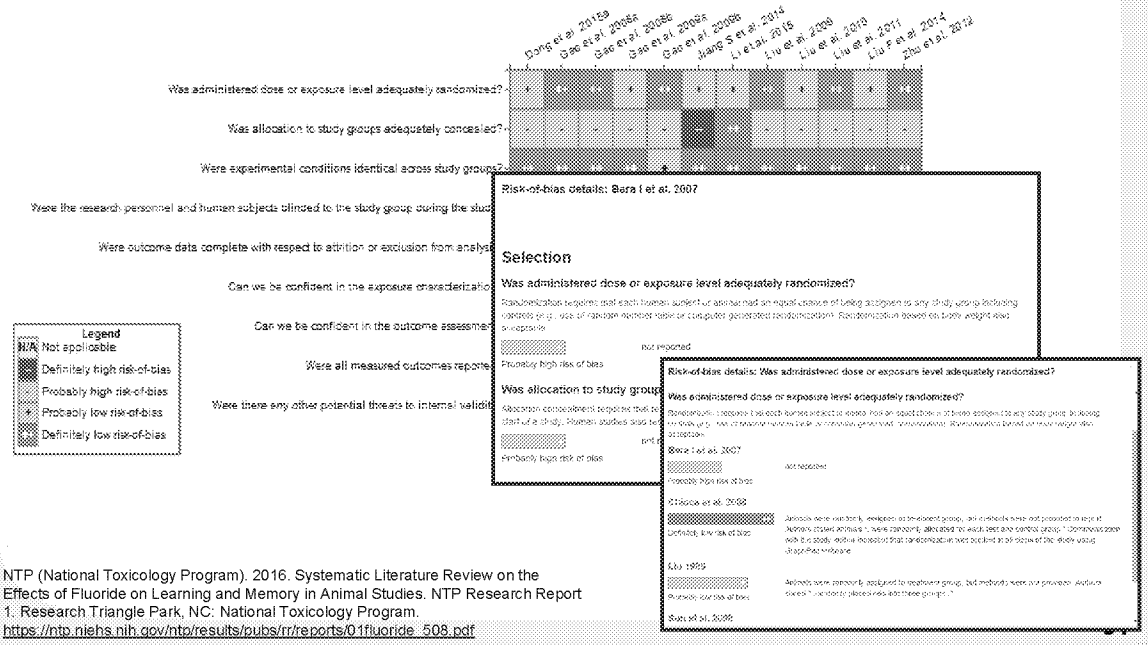
Exposure group	N	Adjusted prevalence ratio	p-value
No folic acid use	1902	1.0	n.a.
Folic acid-only supplements*	1996	0.99 (0.87, 1.09)	n.s.
Pre-natal vitamin supplements	297	1.07 (0.89, 1.29)	n.s.
Multivitamin or vitamin B complex supplements	199	1.04 (0.83, 1.3)	n.s.

* Main finding re-adjusted by RAIVO assessment authors



NTP Monograph: Identifying Research Need
51. http://ntp.niehs.nih.gov/ntp/ohat/folicacid/

HAWC: Risk of Bias



NTP (National Toxicology Program). 2016. Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies. NTP Research Report 1. Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/01fluoride_508.pdf

HAWC: Download Reports

- Entire database for an assessment can be downloaded in Microsoft Excel exports